RESEARCH COMMUNICATION

# Sodium Intake, Salt Taste and Gastric Cancer Risk According to Helicobacter Pylori Infection, Smoking, Histological Type and Tumor Site in China

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## Abstract

**Aim: The risk factors mostly strongly associated with gastric cancer are gastric bacteria *Helicobacter pylori* and diet. Using a case-control study among residents in Jinan, we examined the association between the salt taste and gastric cancer according to *H. pylori* infection, smoking and histological type as well as tumor site. Methods: This population-based case-control study included 207 cases and 410 controls. Data on potential risk factors of gastric cancer were obtained by interview of cases and controls with a questionnaire, salt taste preference was measured for all subjects, and IgG antibodies to *H. pylori* were applied to assess infection. Risk measures were determined using unconditional logistic regression. Results: The proportions of salt taste at intervals of 1.8-7.2 g/L and ≥7.2 g/L were significantly higher in cases than controls, with ORs of 1.56 (1.23-3.64) and 2.03 (2.12-4.11), respectively, subjects with high salt intake having an elevated risk for gastric cancer when infected with *H. pylori*. Significant modification by smoking and tumor site was observed across the different measures of salt intake, the highest salt taste showed higher cancer risk in ever smokers or with non-cardia cancers. Conclusion: Our study supports the view that high intake of sodium is an important dietary risk factor for gastric cancer, with a synergistic effect found between salt and *H.pylori* and smoking, dependent on the tumor site.**

**Keywords:** Gastric cancer - sodium intake - salt taste preference - *H.pylori* infection - tumor site

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## Introduction

About one million new cases of stomach cancer were estimated to have occurred in 2008 (988 000 cases, 7.8% of the total), making it currently the fourth most common malignancy in the world, behind cancers of the lung, breast and colo-rectum. More than 70% of cases (713 000 cases) occur in developing countries (467 000 in men, 246 000 in women), and half the world total occurs in Eastern Asia (mainly in China) (IARC, 2011). In China, gastric cancer is the third cause of death from the most common cancer, with an age-standardized incidence of 21.1 and 15.2 cases per 100, 000 person-years for men and women, respectively, according to the 2008 national cancer statistics (Yang, 2006).

Geographic and ethnic difference, trend in cancer incidence with time, and changes in incidence patterns observed among immigrants indicate that gastric cancer is closely associated with modifiable factors, such as diet. In 2007, salt and salted/salty foods were classified as probable risk factors for gastric cancer (WCRF/AICR, 2007). In experimental studies, with rats, ingestion of salt is known to cause gastritis, and when co-administered, enhance the carcinogenic effect of known gastric carcinogens, such as N-methyl-N-nitro-N-nitrosoguanidine (Fox et al., 1999; Kato et al., 2006). A high intragastric salt concentration destroys the mucosal barrier, and leads to inflammation and damage such as diffuse erosion and degeneration. The induced proliferous change might enhance the effect of food-derived carcinogens. However, the available evidence is mixed, because large numbers of studies used subjective measurement of salt intake, and many important potential modifications were not accounted into analysis, including the synergistic effect between salt and *H.pylori* and smoking.

Few studies presented subgroup analysis according to the histological types, because the environmental factors have a greater influencing on the intestinal than the diffuse type. The association between salt intake and gastric cancers in different topographies may be different due to the etiological difference, also different Helicobacter pylori infection was observed (Huang et al., 1998; HCCG, 2001).

In previous study, a subjective method to measure the salt intake by salt taste preference, and indicated the salt taste could better represent the salt intake (Zhang and Zhang, 2011). In our study, we thereby conducted a case-control study to assess the relationship between the salt taste and gastric cancer according to *H. pylori* infection, smoking and histological type as well as tumor site. We are not aware of any previous study examining such relationship in China.

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## Materials and Methods

We conducted a case-control study of new diagnosed gastric cancer patients admitted to the surgery wards of the Department of oncology of General Hospital of Jinan Military Region. From January 2007 to December 2010, a total of 207 histological confirmed gastric cancer cases, who aged 40-75 years. 436 controls were recruited from health individuals visiting hospital for routine physical examination. Finally, the overall sample comprised 410 controls aged 35-77 years, corresponding to a participation proportion of 94.03%. Controls were eligible for this analysis if there was no malignant tumors or digestive tract disorders free.

Trained interviewers inquired both cases and controls using a structured questionnaire covering demographic, social, behavior and medical characteristics. The dietary habits were recorded using a semiquantitative food frequency questionnaire (FFQ) comprising 65 food items/groups or beverage categories, which have been validated previously. A total of 201 cases declared to have changed their food intake ≥12 months before interview because of gastrointestinal symptoms, and were excluded from this analysis. Cases and controls who had modified their habits during the previous year because of any other previous condition were not excluded, but were asked to recall dietary intake in the year before the change.

A blood sample was drawn and serum was kept frozen at -20 °C. Anti-H. pylori serum IgG titres were quantified by ELISA. Participants were classified as negative if they had <16RU $ml^{-1}$, as borderline if their antibody concentration was between 16 and 22 RU $ml^{-1}$ and as positive if this was ≥22 RU $ml^{-1}$, according to the manufacturer's instructions. In our analysis, subjects with borderline IgG titres were classified as infected. We used two different ways to evaluate salt intake. First, we considered the sodium intake estimated by using the FFQ, considering the food's intrinsic sodium consumed per day. For analysis, the tertiles of sodium or salty foods intake of observed in the controls were used as cutoffs to define groups of exposure. Secondly, we used tested the salty taste preference to evaluate the salt intake in subjects. To measure the threshold level of salty taste, we dropped several NaCl solutions on the tip of the tongue, which was described in previous study (Zhang and Zhang, 2011).

*Statistical analysis*

Diet intake was classified into two categories: < 3 times/week and ≥ 3 times/week. Cigarette smokers were divided into non-smokers and smokers who smoked more than 10 cigarettes per week for at least 6 months; Alcohol drinkers were classified into non-drinkers and drinkers who consumed more than 50 mL of distilled spirits per week for at least 6 months. The sodium intake was categorized into < 3 g/day, 3-5 g/day and >5 g/day. The concentrations of each test NaCl solution were classified into 6 grades from 0.45 g/L to 14.6 g/L with 0.9g/L interval, and the taste of NaCl solution was categorized into < 1.8 g/L, 1.8-7.2 g/L and ≥ 7.2 interval. The unconditional logistic regression was used to calculate odds ratios (OR), and corresponding 95% confidence intervals (CI) for gastric cancer in relation to exposure of interest. The association between salt consumption and gastric cancer was quantified by using crude and gender-, age-, education-, smoking- and *H.pylori* infection-adjusted odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were computed by unconditional logistic regression. Stratified analyses of salt food intake were performed according to H.pylori infection, smoking status and histological type as well as location of cancer. A potential effect modification by H.pylori or smoking was assessed by including interaction terms in the regression models, for infection status (negative or positive) and smoking status (never or ever). All reported trend test significance levels (p-values) were two-sided (Woodward, 1999). STATA, version 10.0 (StatCorp LP, College Station, TX, USA), was used for all the analysis.

## Results

Most of the histological type of cancers were intestinal (61.8%). Few of the cancers were located in cardia region (81.6%). There was no significant difference between cases and controls regarding gender and age. Among cases, 132 (63.7%) of the cases and 258 (62.9%) of the controls were males (Table 1). The average age of cases and controls were 53.1±6.20 and 52.8±5.90 years, respectively. The H.pylori infection was more frequent in cases (82.1%) than in controls (61.4%). The proportion of ever smokers was 63.2% among cases, which was higher than that in controls. No significant difference was found in ever drinking between cases and controls.

The median sodium intake from FFQ in cases was

**Table 1. Characteristics of Patients with Gastric Cancer and Matched Controls**

| Characteristics | Cases (%) N=207 | Controls (%) N=410 | *p* |
|---|---|---|---|
| Age (yr) | 53.1±6.20 | 52.8±5.90 | 0.16 |
| Male, n (%) | 132(63.8) | 258(62.9) | 0.84 |
| Literate, n (%) | 81(39.1) | 189(46.1) | 0.1 |
| Annual income < 5000 RMB, n (%) | 65 (31.4) | 71 (17.3) | <0.001 |
| Ever smoking, n (%) | 131(63.3) | 184(44.9) | <0.001 |
| Ever drinking, n (%) | 67(32.4) | 80(19.5) | <0.001 |
| H.pylori infection Positive, n (%) | 170(82.1) | 252(61.5) | <0.001 |

**Table 2. OR and 95% CIs for Sodium Intake and Salt Taste Preference and GC**

| | Cases (%) N=207 | Controls (%) N=410 | Odds ratio (95% CI) † |
|---|---|---|---|
| Sodium intake (g/day) | | | |
| Mean | 3.89±0.18 | 3.15±0.14 | - |
| <3 | 47(22.7) | 115(28.1) | 1.0 (Reference) |
| 3~5 | 108(52.2) | 213(51.9) | 1.78(1.17-2.19) |
| >5 | 52(25.1) | 82(20.0) | 2.45(1.623.57) |
| Salt taste preference | | | |
| <1.8 | 58(28.1) | 134(32.7) | 1.0 (Reference) |
| 1.8-7.2 | 103(49.8) | 193(47.1) | 1.56(1.23-3.64) |
| >7.2 | 46(22.2) | 83(20.2) | 2.03(2.12-4.11) |

†OR was adjusted for sex, age, education level, smoking, drinking and H.pylori infection

**Table 3. Association Between Salt Intake and Preference and Gastric Cancer According to *H.pylori* Infection**

| | Odds ratio (95% CI) † *H.pylori* infection | | p for |
|---|---|---|---|
| | Negative | Positive | interaction |
| Sodium intake (g/day) | | | |
| <3 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 3~5 | 1.10(0.34-2.62) | 2.43(1.21-3.23) | |
| >5 | 1.81(0.95 -2.12) | 5.34(2.65-8.94) | |
| Salt taste preference(g/L) | | | |
| <1.8 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 1.8-7.2 | 1.23(0.79-4.01) | 2.89(1.64-5.32) | |
| >7.2 | 1.93(0.97 -2.43) | 6.31(3.03-11.1) | |

†OR was adjusted for sex, age, education level, smoking and drinking

**Table 4. Association Between Salt Intake and Preference and Gastric Cancer According to Smoking Status**

| | Odds ratio (95% CI) † Smoking status | | p for |
|---|---|---|---|
| | Never smokers | Ever smokers | interaction |
| Sodium intake (g/day) | | | |
| <3 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 3~5 | 1.23(0.61-1.55) | 1.87(1.17-3.12) | |
| >5 | 1.52(1.13-2.78) | 3.56(1.65-5.27) | |
| Salt taste preference(g/L) | | | |
| <1.8 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 1.8-7.2 | 1.34(0.89-4.31) | 2.12(1.35-4.71) | |
| >7.2 | 1.89(2.55-3.36) | 4.12(2.89-9.83) | |

†OR was adjusted for sex, age, education level, drinking and H.pylori infection

**Table 5. Association Between Salt Intake and Preference and Gastric Cancer According to Histological Types**

| | Odds ratio (95% CI) † Histological types | | p for |
|---|---|---|---|
| | Intestinal | Diffuse | interaction |
| Sodium intake (g/day) | | | |
| <3 | 1.0 (Reference) | 1.0 (Reference) | 0.48 |
| 3~5 | 1.02(0.32-1.50) | 1.16(0.37-1.63) | |
| >5 | 2.14(1.13-3.13) | 2.29(1.20-3.45) | |
| Salt taste preference(g/L) | | | |
| <1.8 | 1.0 (Reference) | 1.0 (Reference) | 0.37 |
| 1.8-7.2 | 1.29(0.38-2.13) | 1.15(0.46-2.16) | |
| >7.2 | 2.37(1.45-3.54) | 2.16(1.30-3.32) | |

†OR was adjusted for sex, age, education level, smoking, drinking and H.pylori infection

**Table 6. Association Between Salt Intake and Preference and Gastric Cancer According to Tumor Sites**

| | Odds ratio (95% CI) † Tumor sites | | p for |
|---|---|---|---|
| | Non-cardia | Cardia | interaction |
| Sodium intake (g/day) | | | |
| <3 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 3~5 | 1.44(0.55-1.89) | 1.20(0.50-1.77) | |
| >5 | 2.59(1.28-3.07) | 1.64(0.86-2.23) | |
| Salt taste preference(g/L) | | | |
| <1.8 | 1.0 (Reference) | 1.0 (Reference) | <0.05 |
| 1.8-7.2 | 1.50(0.59-1.67) | 1.32(0.65-1.56) | |
| >7.2 | 2.42(1.19-3.36) | 1.72(0.88-2.37) | |

†OR was adjusted for sex, age, education level, smoking, drinking and H.pylori infection

3.89±0.18 g/day, which was higher than that in controls (3.15±0.14 g/day). The proportion of salty taste below 1.8 g/L in cases were significantly lower than that in controls, and proportions of salt taste at the interval of 1.8-7.2 g/L and ≥ 7.2 g/L were significantly higher than controls, and with the ORs of 1.56 (1.23-3.64) and 2.03 (2.12-4.11), respectively. Especially for salt taste above 7.2 g/L, a heavy risk of esophageal cancer was found.

Despite the suggestion of a strong association with salt exposure among the H.pylori infected (Table 3), significant differences in the highest salt taste were observed among H. pylori positive (e.g., highest vs lowest sodium intake from FFQ: OR=5.34, 95% CI: 2.65-8.94, P for interaction: 0.012; From salt taste preference: OR=6.31, 95% CI: 3.03-11.1; p for interaction < 0.05), however, no significant differences were observed for other measures of salt exposure among H. pylori negative. Significant modification by smoking was observed across the different measures of salt intake, the highest salt taste showed higher risk in ever smokers (e.g., highest vs lowest sodium intake from FFQ: OR=3.56, 95% CI: 1.65-5.27, p for interaction<0.05; From salt taste preference: OR=4.12, 95% CI: 2.89-9.83; p for interaction<0.05; Table 4). No effect modification by histological type was found in different salt taste (Table 5). However, significant variations in esophageal cancer risk associated with salt taste were observed by tumor site (e.g., highest vs lowest sodium intake from FFQ: OR=2.59, 95% CI: 1.28-3.07 for non-cardia cancers; From salt taste preference: OR=2.42, 95% CI: 1.19-3.36; p for interaction<0.05; Table 6).

## Discussion

The present population based case-control study has demonstrated that the dietary sodium intake, which assessed by different methods, were independently associated with increased gastric cancer risk, and modified by H.pylori infection, smoking and tumor site.

The increased risk from high sodium intake in gastric cancer might be because of compounds other than salt that are produced during the preservation process. High salted food, such as processed meat, pickled vegetable or dried fish, whose consumption is used as a surrogate for salt exposure, also have a high content of nitrosated compounds. Ingestion of those high salted food could induce gastritis and coadministrate with N-methyl-N-nitro-N-nitrosoguanidine to enhance the carcinogenic effect of gastric carcinogens (Tatamatsu et al., 1975; Takahashi and Hasegawa, 1985). A high intragastric salt concentration could destroys the mucosal barrier, and leads to inflammation and damage such as diffuse erosion and degeneration. The induced proliferous change might enhance the effect of food-derived carcinogens (WCRF/AICR, 2006). Our study observed the salt intake increased the gastric cancer risk, supporting the role of salt and nitrosated compounds in gastric carcinogenesis.

Salt preference were estimated by 24-h sodium in urine or questionnaire. Excretion of sodium in urine over a 24-h period could reflect accurately the sodium ingested from different sources, but this method cannot be used respectively in case-control studies. The salt preference

investigated by questionnaires could not accurately reflect the salt intake and taste preference, because the levels reported as high in one study might be considered low estimated in other studies due to the different scales of salt intake evaluation. Previously, the salt taste preference showed high relationship to the salt intake from FFQ, and could better represented the sodium intake of subjects (Zhang and Zhang, 2011). In this study, we found the salt intake from FFQ had the similar risk factors according to different H.pylori infection, smoking, histological type and tumor site, which indicated the salt taste preference could be better represented the salt intake. Moreover, NaCl solution taste experiment could spend less time and cost, and gained a more subjective information of salt intake. Also, this experiment may be more acceptable for patients due to spend less time than FFQ investigation.

The proposed mechanisms which salt can cause gastric cancer either direct damage to the gastric mucosa leading to hyperplasia of the gastric pit epithelium with increased potential for mutations or effect of interaction with *H.pylori*, as the damage caused by salt may also increase gastric *H.pylori* colonization (Nozaki et al., 2002; Yang, 2006). This suggests there may be interaction between sodium intake and H.pylori infection, and this was confirmed in our study. Moreover, a synergistic effect might be occurred if any gastric mucosa damage by salt was enhanced by tobacco carcinogens (Iwata et al., 1995). A significant modification was observed across different measures of salt intake regarding smoking status.

The development of non-cardia is thus considered to be a multistage process with *H.pylori* infection initially inducing superficial gastritis which then progresses to atrophic gastritis, in turn progressing to dysplasia and then frank cancer (Correa, 1992). The factors which are thought to contribute to the development of non-cardia cancer including dietary and environmental factors as well as H.pylori infection. However, cancer of the cardia region of the stomach shows no consistent association with H.pylori, and this cardia cancers show similarities with esophageal adenocarcinoma and may in fact be such cancers which arise from the most distal esophagus. Damage to the most distal esophagus by reflux of gastric acid causes columnar metaplasia, intestinal metaplasia, dysplasia and cancer, and it may be regarded to be the mechanism by which cardia cancer develops (Hansen et al., 2005). Our study observed a significantly interaction between tumor site and salt intake in gastric cancer risk, which indicated the different etiology of tumor site. Potential limitations should be considered in our study. Firstly, cases may provide a underestimated report of their past dietary habits, because the changes in past dietary habits due to disease. Therefore, the cancer risk of salt intake may be underestimated. Secondly, confounding factors is unlikely to be a major concern, and the main potential confounders should be considered into account. Further adjustment for fruit and vegetables intake, and total or red/processed meat consumption did not change conclusions. We did not consider the physical activity or body mass index on esophageal cancer, and these potential factors should be taken into account in further studies.

Our study indicated that the high intake of sodium intake is an important dietary risk factor for gastric cancer, and a synergistic effect was found between salt and H.pylori, smoking and tumor site.

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